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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte YOSHIHITO IKEDA and HIROMI SATOU

Appeal 2010-005910
Application 10/018,770
Technology Center 1600

Before CAROL A. SPIEGEL, TONI R. SCHEINER, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 4, 6-8, 10-14, and 19. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

"The present invention relates to a drug composition containing a lecithin-modified superoxide dismutase (hereinafter . . . PC-SOD) and a drug carrier, particularly sucrose" (Spec. 1).

According to the Specification, combining PC-SOD with "a drug carrier, particularly sucrose, inhibits a reduction of PC-SOD activity due to long term storage (maintains stability); retains good property when lyophilized; has an action of controlling appearances of peaks of analogues when analyzed by column chromatography" (Spec. 2).

Claims 1, 4, 6-8, 10-14, and 19, all the claims pending, are on appeal. The claims have not been separately argued, and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative:

1. A drug composition comprising sucrose and a lecithin-modified superoxide dismutase represented by the following general formula (I):

$SOD'(Q\text{-}B)_m$

wherein SOD' is a residue of superoxide dismutase, Q is a chemical crosslinking; B is a residue without a hydrogen atom of a hydroxyl group of lysolecithin having the hydroxyl group at the 2-position of glycerol; m is an average number of bonds of lysolecithin to one molecule of superoxide dismutase which is a positive number of 1 [or] more.

Claims 1, 4, 6-8, 10-14, and 19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Mizushima[2] in view of Fukui.[3]

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[2] Japanese Patent Application JP 9-117279 A of Yutaka Mizushima et al., published May 6, 1997 (all references are to the English language translation).

[3] Japanese Patent Application JP 1-304882 of Kiyoshi Fukui et al., published December 8, 1989 (all references are to the English language translation).

ISSUE

The issue raised by this appeal is whether the Examiner has established that one of ordinary skill in the art would have had a reason to include sucrose in a pharmaceutical composition comprising lecithin-modified superoxide dismutase, given the teachings of Mizushima and Fukui.

FINDINGS OF FACT (FF)

1. The Specification provides SEQ ID NO:1, the 153 amino acid sequence of the human Cu/Zn superoxide dismutase (SOD), and teaches that "the actual human Cu/Zn SOD is constituted as a dimer of protein having this amino acid sequence" (Spec. 8).

2. The Specification teaches that combining PC-SOD with "a drug carrier, particularly sucrose, inhibits a reduction of PC-SOD activity due to long term storage (maintains stability); retains good property when lyophilized; has an action of controlling appearances of peaks of analogues when analyzed by column chromatography" (Spec. 2). "The analogues . . . comprise various substances generated by cleavage at various sites in mainly lecithin including liberated fatty acids" (*id.* at 16).

3. Mizushima discloses a pharmaceutical composition comprising lecithin-modified superoxide dismutase "in the water for injection dissolved in a buffer, the isotonic medicine, the pH regulator, the stabilizer . . . prepared by dispensing . . . and freeze-drying" (Mizushima ¶ 28).

4. Mizushima does not disclose any stabilizer in particular for the pharmaceutical composition.

5. Kinoshita[4] summarizes several reports describing the properties of PC-SOD, including a report that describes PC-SOD as "useful as an anti-inflammatory agent without adverse effect such as antigenicity" (Kinoshita, col. 1, ll. 42-61).

6. Fukui reports the molecular weight of human SOD monomer to be 20 kD as determined by denaturing polyacrylamide gel electrophoresis (Fukui 7). This is reasonably consistent with Kinoshita, which reports that "[t]he molecular weight of monomer of PC-SOD subunit (PC-SOD is a homodimer of the subunit) was determined by SDS-polyacrylamide gel electrophoresis to be about 18000" (Kinoshita, col. 7, ll. 36-40).

7. The Examiner asserts, and Appellants do not dispute, that the active form of human SOD, like PC-SOD, is a homodimer, and "the active form of the underivatized enzyme can range from about 32 to 40 kD," depending on the measurement technique used (Ans. 7).

8. Fukui teaches that "[m]ost proteins are known to generate by-products, undergo denaturation rendering them insoluble and the like, and lose their biological activity when subjected to freezing and thawing or freeze-drying processes" (Fukui 3).

9. Fukui reports that "[d]enaturation of bovine SOD is 25 percent or greater with freeze drying," but can be prevented "by combining pentose and hexose (for example, galactose, fructose, fucose, arabinose, glucose, mannose, and sucrose) with bovine SOD prior to freeze-drying" (Fukui 4).

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[4] U.S. Patent 5,762,929, issued to Kinoshita et al. on June 9, 1998. This reference was submitted by Appellants with an Information Disclosure Statement filed July 27, 2005, and considered by the Examiner on August 10, 2005.

10. On the other hand, according to Fukui:

> No decrease in the enzymatic action of human SOD is observed when this protein is subjected to freezing and thawing or freeze-drying processes, nor is formation of insoluble matter visible to the naked eye. However, human SOD subjected to analysis by sodium dodecyl sulfate-polyacrylamide electrophoresis, high-performance gel filtration liquid chromatography, and the like produces by-products consisting mostly of dimers.

(Fukui 3.)

11. Fukui teaches that the human SOD monomer is 20 kD, and active SOD (the homodimer) is 40 kD, while the by-products are 40 kD and 79 kD (Fukui 7-8). These "by-products resulting from the storage process may have allergenic side effects; [thus] the generation of such substances must be prevented" (Fukui 3).

12. Fukui teaches that combining human SOD with a disaccharide (e.g., sucrose), a ketose monosaccharide (e.g., fructose), or a sugar alcohol (e.g., mannitol) prior to freeze-drying or multiple freeze-thaw cycles inhibits the formation of the 40 kD and 79 kD by-products (Fukui 5; Tables 1-3). However, adding "aldose monosaccharides such as galactose, arabinose, glucose and the like to human SOD" prior to freeze-drying actually promotes denaturation, and should be avoided (*id.* at 4).

13. In Embodiment 3 of Fukui, "[t]he stability of human SOD . . . was examined" after freezing and thawing. Human SOD was combined with sucrose at a ratio of 1:2 prior to subjecting the mixture to multiple rounds of freezing and thawing. No denaturation of the human SOD was observed, and only a minimal amount of the undesirable 79 kD by-product was detected (Fukui 9; Embodiment 3).

14. In Embodiment 9 of Fukui, "[t]he stability of freeze-dried human SOD with the addition of sugar was examined." Human SOD was combined with sucrose, again at a ratio of 1:2, prior to subjecting the mixture to freeze-drying. No denaturation of the human SOD was observed, and only minimal amounts of the undesirable 40 kD and 79 kD by-products were detected (Fukui 13; Embodiment 9).

DISCUSSION

Mizushima discloses a freeze-dried composition comprising lecithin-modified superoxide dismutase, water, buffer, a pH regulator, and a stabilizer, but doesn't specify any stabilizer in particular (Mizushima ¶ 28; FF3, 4).

Fukui teaches that freeze-drying bovine SOD (i.e., unmodified SOD) causes denaturation which can be largely prevented by combining the SOD with various sugars, including sucrose, prior to freeze drying (FF9). In addition, Fukui teaches that freeze-drying human SOD doesn't cause denaturation, but does produce allergenic by-products of 40 and 79 kD, which can be minimized by combining the human SOD with a disaccharide (e.g., sucrose), a ketose monosaccharide, or a sugar alcohol prior to freeze-drying (FF10, 12). On the other hand, Fukui specifically warns against combining human SOD with aldose monosaccharides, as these actually promote degradation (FF12).

The Examiner concluded that:

> [T]he artisan of ordinary skill seeking to store the SOD derivatives of [Mizushima], recognizing from [Fukui] that addition of sucrose would improve the storage stability of the SOD derivatives, clearly would have been motivated by [Fukui] to have combined the SOD derivatives of [Mizushima] with sucrose to have rendered them stable for storage. A reasonable

> expectation of success would have been based on the fact that [Fukui] discloses that the very same enzyme was rendered storage stable by combination with sucrose.

(Ans. 4.)

We agree with the Examiner's rationale and conclusion, as well as the Examiner's response to Appellants' arguments (as set forth on pages 4-14 of the Examiner's Answer).

Essentially, Appellants contend that "[t]here is an absence of any suggestion in the prior art that PC-SOD is susceptible to denaturation, that dimerization of PC-SOD is undesirable, or that PC-SOD dimers have allergenic side effects" (App. Br. 5). In any case, Appellants contend that Fukui's "disclosed purpose of adding sucrose to SOD is to prevent dimerization (the chemical combination of two monomers) of SOD and the associated allergenic side effects, not to prevent denaturation (which is the uncoiling of the SOD into an inactive conformation)" (Reply Br. 3). In addition, Appellants point to column 1, lines 51-69 and column 7, line 38 of Kinoshita as evidence that it was known that "PC-SOD does not exhibit allergenic side effects, although it already 'is a homodimer'" (App. Br. 5-6). "Thus," Appellants contend, "the motivation disclosed in . . . [Fukui] for adding a stabilizer such as sucrose to SOD is not present with PC-SOD" (*id.* at 5-6).

These arguments are not persuasive. With the exception of claims 7 and 8, the claims are not even limited to the human enzyme, and the Examiner's conclusion that one of ordinary skill in the art would have expected bovine PC-SOD to be denatured upon freeze-drying is reasonable, given the fact that denaturation was known to be a problem with the bovine unmodified enzyme (FF9). The Examiner's conclusion that one would also

have expected formation of undesirable by-products with freeze-dried human PC-SOD (even if denaturation would not have been expected) is similarly reasonable, given the fact that allergenic by-products were known to be a problem with the unmodified enzyme (FF10). Moreover, Fukui provides evidence that freeze-drying was known to cause problems with "[m]ost proteins" (FF8). Given these expectations, we agree with the Examiner that one of ordinary skill in the art would have had a reason to add sucrose to PC-SOD, whether human or bovine.

Moreover, we disagree with Appellants' contention that Fukui's purpose in adding sucrose to SOD is to prevent dimerization of the SOD monomers. As discussed above, the active form of the enzyme is a homodimer (FF1, 6, 7). Fukui's purpose in adding sucrose to human SOD is to prevent the formation of allergenic 40 kD and 79 kD by-products of freeze-drying (FF12). While Fukui describes these by-products as dimers (or possibly even dimers of dimers, i.e., tetramers), they are clearly not the active homodimeric form of the enzyme - Fukui would not have referred to them as by-products of the freeze-drying process otherwise.

Nor are we persuaded that Kinoshita belies the Examiner's proposed reason or motivation for combining sucrose with PC-SOD. First, the homodimer Kinoshita refers to in columns 1 and 7 is plainly the active form of the enzyme (FF5, 6), not a by-product of freeze-drying, so the fact that Kinoshita states that PC-SOD is "useful as anti-inflammatory agent without adverse effect such as antigenicity" (FF5) is not evidence that freeze-dried preparations of PC-SOD were known to be non-allergenic. Indeed, there is no indication whatsoever that these portions of the reference have anything to do with administration of freeze-dried PC-SOD.

Finally, Appellants contend that they "have discovered that there is a loss of biological activity of PC-SOD during freeze-drying and/or freeze-thaw cycles due only to degradation of the phosphatidylcholine (PC) moieties" (App. Br. 8). Appellants contend that one "cannot learn from the prior art that loss of activity associated with lyophilization and storage of PC-SOD is caused by degradation of the PC moieties, or that such degradation is prevented by adding sucrose" (Reply Br. 10), thus, "the entire motivation for the claimed invention, can only be found in Appellants' specification" (*id.*).

This argument is not persuasive. First, Appellants have not pointed to any support in the Specification for the contention that loss of biological activity is exclusively due to degradation of the PC moieties on the derivatized SOD. Second, as long as some suggestion to combine the elements is provided by the prior art as a whole, the law does not require that they be combined for the reason or advantage contemplated by the inventor. *See e.g., In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992); *In re Kronig*, 539 F.2d 1300, 1304 (CCPA 1976). The recognition that sucrose prevents cleavage of lecithin does not make it any less obvious to use sucrose to stabilize PC-SOD, whether bovine or human, for the reasons proposed by the Examiner.

CONCLUSION

The Examiner has established that one of ordinary skill in the art would have had a reason to include sucrose in a pharmaceutical composition comprising lecithin-modified superoxide dismutase.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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